STUDY CP-97-012

Title: Phase II Study of Iodine I 131 tositumomab for Non-Hodgkin's Lymphoma Patients who Have Previously Received Rituximab.

Design: Phase 2, single-arm, open-label, multicenter study of iodine I 131 tositumomab in the treatment of non-Hodgkin's lymphoma patients who were previously treated with rituximab therapy without an objective response or who relapsed/progressed during or within 6 months following therapy.

Accrual initiated – July 17, 1998
Closed to enrollment - November 19, 1999
Data-cutoff – December 17, 2000
Final study report: August 17, 2001
Data cut-off: February 8, 2002

Principal investigators and study sites

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Objectives

1. To assess the response rate and duration of response of iodine I 131 tositumomab therapy in patients who were previously treated with at least 4 doses of rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.
2. To assess the safety of Iodine I 131 -tositumomab therapy in patients who were previously treated with at least 4 doses of Rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.

Inclusion Criteria (verbatim from protocol after the inclusion of amendments 1-4)

1. Patients must have a histologically confirmed initial diagnosis of low grade non-Hodgkin's B-cell lymphoma according to International Working Formulation (i.e., small lymphocytic [with or without plasmacytoid differentiation]; follicular, small-cleaved; or follicular, mixed small-cleaved lymphoma), low-grade lymphoma that has transformed to higher grade histology, or *de novo* follicular large cell lymphoma.
2. Patients must have evidence that their tumor tissue expresses the CD20 antigen. Immunoperoxidase stains of paraffin-embedded tissue showing positive reactivity with ---- antibody or immunoperoxidase stains of frozen tissue showing positive reactivity with Anti-B1 Antibody or evidence of CD20 positivity by flow cytometry are acceptable evidence of CD20 positivity.
3. Patients must have been treated with at least 4 doses of rituximab at any time and failed to achieve an objective response (CR, CCR, PR), or relapsed/progressed during treatment or following the completion of rituximab therapy.
4. Patients must have a performance status of at least 60% on the Karnofsky Scale and an anticipated survival of at least three months.
5. Patients must have an absolute granulocyte count >1500/mm^3 (US) or >1500 x 10^9/l (UK)and a platelet count >100,000/mm^3 (US) or >100,000 x 10^9/l (UK) within 14 days

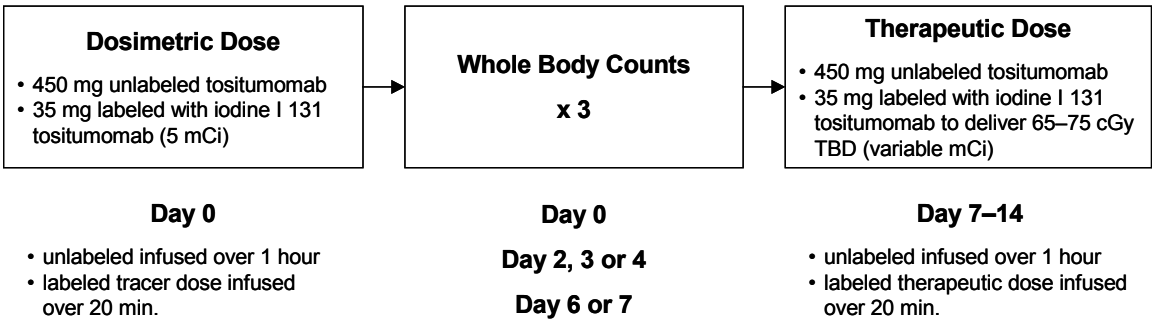
of study entry. These blood counts must be sustained without support of hematopoietic cytokines or transfusion of blood products.

6. Patients must have adequate renal function (defined as serum creatinine <1.5 x upper limit of normal) and hepatic function (defined as total bilirubin <1.5 x upper limit of normal and hepatic transaminases [AST and ALT] <5 x upper limit of normal) within fourteen days of study entry.
7. Patients must have bi-dimensionally measurable disease. At least one lesion must be 2 x 2 cm (by CT scan).
8. Patients must be at least 18 years of age.
9. Patients must give written informed consent and sign an Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form prior to study entry.

Exclusion Criteria (verbatim from final protocol which includes amendments 1-4)

1. Patients with more than an average of 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically within 42 days of study entry. Bilateral posterior iliac crest core biopsies are required if the percentage of intratrabecular space involved exceeds 10% on a unilateral biopsy. The mean of bilateral biopsies must be no more than 25%.
2. Patients who have received cytotoxic chemotherapy, radiation therapy, immunosuppressants, or cytokine treatment within 4 weeks prior to study entry (6 weeks for nitrosourea compounds) or who exhibit persistent clinical evidence of toxicity. The use of systemic steroids must be discontinued at least 1 week prior to study entry.
3. Patients with prior hematopoietic stem cell transplant following high dose chemotherapy or chemo/radiotherapy.
4. Patients with active obstructive hydronephrosis.
5. Patients with evidence of active infection requiring intravenous (IV) antibiotics at the time of study entry.
6. Patients with New York Heart Association class III or IV heart disease (see Appendix D) or other serious illness that would preclude evaluation.
7. Patients with prior malignancy other than lymphoma, except for adequately treated skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for 5 years.
8. Patients with known HIV infection.
9. Patients with known brain or leptomeningeal metastases.
10. Patients who are pregnant or breastfeeding. Patients of childbearing potential must undergo a pregnancy test within 7 days of study entry and radiolabeled antibody is not to be administered until a negative result is obtained. Males and females must agree to use effective contraception for 6 months following the radioimmunotherapy.
11. Patients with previous allergic reactions to iodine. This does not include reacting to IV iodine-containing contrast materials.
12. Patients who previously received radioimmunotherapy.
13. Patients with progressive disease within 1 year of irradiation arising in a field that has been previously irradiated with >3500 cGy.
14. Patients who are HAMA positive.
15. Patients who are concurrently receiving either approved or non-approved (through another protocol) anti-cancer drugs or biologics.

Treatment Plan



Patient Monitoring Plan

Data were collected in three different phases.

1. During the initial study period, patients had data collected during outpatient visits
   - Imaging at several time points over days 0-7 to collect dosimetry data
   - AE data was collected at each visit.
   - Hematologic values were required to be obtained at baseline, weeks 3 though 9, weeks 13 and 25 and thereafter every 26 weeks during the follow-up phase.
   - HAMA values were obtained at baseline, day 5, weeks 7, 13, and 25.
   - Thyroid function (including TSH) data were obtained at baseline, week 25 and during follow up and long-term follow up (after amendment 4) visits.
   - Tumor response was evaluated at baseline and at weeks 7, 13, 25, and during follow-up visits.

2. At week 52, the follow up [FU] phase of visits began every 26 weeks until two years or until the patient withdrew from the study or two years elapsed. Follow up visits included physical examination and history, hematology and serum chemistry and thyroid function tests, radiographic evaluations, information on AEs and medication experience, and bone marrow studies if baseline biopsy was positive for lymphoma.

3. The last phase of monitoring was long-term follow up [LTFU]. LTFU began either after a patient withdrew from study for progressive disease or concomitant therapy or after two years post therapeutic dose. Data was collected every six months. LTFU data initially included only vital status, cancer status, and thyroid function but was expanded in amendment four to include HAMA, TSH sampling and thyroid disease information, second malignancy information and subsequent therapy for NHL by history.

Original Analytic plan

No primary endpoint was identified. The following endpoints were listed: response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. The sample size of 20 patients was selected to enable the response rate to be estimated with a maximum standard error of 0.112 and an expected standard error of 0.10. Point estimates with two-sided 95% confidence intervals would be generated for response rates; patients withdrawing due to death or toxicity before their [response] status could be assessed were considered to have progressive disease (intent-to-treat analysis). Additional analyses of response rates in patients who

completed protocol-specified therapy would also be conducted. Kaplan-Meier curves would be generated for time to event analyses (response duration, time to progression, time to treatment failure and overall survival) and mean and median durations for the time to event analyses reported. Adverse events would be summarized by relationship to study drug, organ system and severity. Summaries of patient discontinuations would be provided. The use of supportive care such as CSFs and transfusions would be provided.

Amendments to the Protocol and amendment date

Amendment # 1 ----------

- Sample size increased from 20 to 40 patients.
- Eligibility (Section 3.1 of protocol) - granulocyte (>1500/ mm3) and platelet (>100,000/ mm3) counts may be obtained within 14 days prior to study entry rather than within 7 days of study entry (inclusion criteria # 5).
- Eligibility- (Section 3.1 of protocol)- renal and hepatic function times of collection not specified in initial submission. Amendment specifies renal and hepatic function studies be obtained within 14 days of study entry.
- Definition of duration measures changed from start of treatment (i.e., administration of dosimetric dose) to date of enrollment.
- Stratified analysis of response by prior response to rituximab was added to the statistical plan.

Amendment #2 ----------

- Inclusion criteria for CD20 positive tumor modified to remove requirement that ≥50% malignant cells are CD20 positive.
- Removed sentence from evaluations (Section 4 of original submission) which stated that patients who achieved a response had to have a confirmatory evaluation 4 weeks later.
- Follow up defined as starting week 52. As in original submission, visits were scheduled every 26 weeks until two years or progressive disease (withdrawal of patient).
- HAMA assay was previously listed as performed at site and now may be done at either on-site or in a Central laboratory.
- Guidelines for Use of CSF found in Appendix E of protocol modified to read “In adults , the recommended CSF doses are 5 micrograms/kg/d of granulocyte-CSF (G-CSF; filgrastim or lenograstim) or 250 micrograms/m^2/d of granulocyte-macrophage-CSF (GM-CSF;sargramostim or molgramostim)”.
- Added sites in the United Kingdom as additional study sites.

Amendment 3 ----------

- New address for sponsor and change in vial size.

Amendment 4 ----------

- Time to treatment failure deleted from study endpoints

- Masked Independent Randomized Radiographic and Oncologic Review Panel (MIRROR panel) was not included in original submission. The MIRROR panel was added to protocol and will consist of two reviewers (radiologist and an oncologist) as described in other studies. Panel will determine response, confirmed response, CR, confirmed CR, duration of response, confirmed duration of response, TTP, time to death.
- Long term follow-up (LTFU) in original submission included only disease status, vital status and thyroid function. Additional data to be collected now include history of myelodysplastic disease or other malignancies, history thyroid medication, subsequent medications for NHL, TSH and HAMA.
- Administrative changes as a result of merger between Coulter and Corixa.

Results

Patient Enrollment and Disposition

Forty-three patients were enrolled between July 17, 1998 and November 19, 1999. Three patients did not receive either the dosimetric or therapeutic dose (012-035-005; 012-036-011; and 012-037-013). Forty patients received both the dosimetric and therapeutic dose.

ENROLLMENT BY PROTOCOL AMENDMENT

	Amendment date	Effective date	Cumulative enrollment
Original protocol	----------	----------	0
Amendment 1	----------	----------	0
Amendment 2	----------	----------	23
Amendment 3	----------	----------	29
Amendment 4	----------	----------	43

Six patients withdrew from the study in the first 90 days. These six patients included three patients who died before day 90 (012-035-008 died day 51; 012-036-005 died day 66 and 012-037-005 died day 35 [see patient précis at end report]). Four of the six patients had chemotherapy within a short period of time. The reason cited for removal from study was disease progression in all 6 patients.

- 012-035-005: Patient withdrew for progressive disease after registration and prior to receipt of dosimetric or therapeutic dose.
- 012-036-011: Patient withdrawn because he was still responding to prior rituximab therapy
- 012-037-013: patient withdrew to seek alternative therapy

<u>Deaths within the first 90 days of study entry</u>

- 012-035-008: Tumor lysis syndrome, hypoxia, hypercalcemia, death (study day 51)
- 012-036-005: Death on study day 66

- 012-037-005: Death on study day 35 due to aspiration pneumonia

Conduct of the Study

BioResearch Monitoring

FDA did not conduct on-site audits of the clinical data obtained under this study at any of the study sites

Financial Disclosures:

None of the principal investigators for this study had financial arrangements with the sponsor that required reporting.

Protocol Violations:

Twenty-one of the 43 patients enrolled (49%) had one or more protocol violations (total of 29 separate protocol violations). Protocol violations were classified by the sponsor in the following categories as entry, concomitant medication, withdrawl and treatment violations. The 8 treatment and 21 entry violations are listed in the table below.

Entry violations compromised the ability to assess the tositumomab therapeutic regimen activity in 5 patients. These included 2 patients who lacked measurable lesions, two patients without radiographic baseline studies, and one patient who was still responding to prior rituximab therapy.

Among the most serious treatment violations were two patients (012-037-003 & 012-036-005) who were seropositive for HAMA on study day 5 and received the therapeutic dose of I 131 tositumomab despite the HAMA results and two patients who were non-compliant for Lugol's solution (012-037-005 & 012-35-007) administration. The two patients who were seropositive for HAMA died on day 112 and 66 respectively and there are limited safety data of the impact of this violation. Neither patient was reported to have had infusional reactions. The patient who was non-compliant with Lugol's solution administration had an elevated TSH at baseline; no other TSH data were available. The second non-compliant patient, 012-035-007, had dosimetric and therapeutic dose infusional reactions, but had normal TSH values post-treatment.

Patient ID	NHL grade	CGY*	Study day	Violation type	Violation description
No measurable tumor sites					
012-035-005	T	0	na	Entry	No tumor measuring 2x2 cm or > at baseline
012-037-001	L	65	-10	Entry	No tumor measuring 2x2 cm or > at baseline
Failure to obtain radiologic studies at appropriate time					
012-035-011	L	75	-38	Entry	Chest, abdomen and pelvis CT scans not done within 28 days of enrollment; performed day 29
012-036-001	L	75	-34	Entry	Head/neck and chest CT scans were not done within 28 days of enrollment; performed day 29
012-036-002	L	75	-17	Entry	Chest CT scan was not done at baseline; no report chest x-ray baseline, weeks 7,13,25
012-036-006	I	75	-2	Entry	Chest, abdomen and pelvis CT scans were not done at baseline; first entry of chest x-ray week 7

Violations of eligibility or timing of data collection					
012-037-005	T	75	15	Entry	Therapeutic dose not within 6-14 days of dosimetric dose due to hypercalcemia
012-037-006	I	65	15	Entry	Therapeutic dose not received within 6-14 days of dosimetric dose
012-037-015	L	75	0	Entry	Dosimetric dose received more than 10 days after enrollment
012-035-015	T	75	-14	Entry	Pregnancy test done greater than 7 days prior to enrollment
012-035-003	T	65	0	Entry	Dosimetric dose date is > 10 days after enrollment date
012-037-004	I	75	-23	Entry	Hematology done > 14 days prior to enrollment
012-037-002	T	75	-6	Entry	Patient had a prior bone marrow transplant 1993
012-037-002	T	75	-6	Entry	Initial diagnosis of diffuse large cell lymphoma from lymph node bx on 5/17/91
012-037-004	I	75	-6	Entry	History of prostate carcinoma in 10/94
012-035-008	L	75	-6	Entry	Patient received 4 weeks of electron beam therapy within 4 weeks of enrollment
012-035-005	T	0		Entry	Progression within previously irradiated field (Patient did not receive drug)
012-036-001	L	75	-34	Entry	Unilateral BM biopsy showed tumor involvement 25%; bilateral biopsy not done
012-036-008	L	75	-14	Entry	ANC 1490 at baseline
Informed consent					
012-037-001	L	65	-2	Entry	Enrolled prior to signing consent (signed consent prior to receiving study drug)
012-037-003	T	75	-6	Entry	Enrolled prior to signing consent (signed consent prior to receiving study drug)
Nuclide violations					
012-037-005	T	75	21	Treatment	Iodide noncompliance, all meds stopped when patient intubated and sent to ICU
012-035-007	T	75	16	Treatment	Patient missed 3 days of SSKI secondary to GI upset
012-035-012	L	75	28	Treatment	Therapeutic dose not within 6-14 days of dosimetric dose due to delay at Nordion supplier
012-036-007	L	75	14	Treatment	Difference between prescribed and actual mCi dose > 10%
012-036-010	L	75	0	Treatment	Time started for Day 0, Day 2 and Day 6 background counts (dosimetry) unknown
HAMA					
012-036-001	L	75	12	Treatment	HAMA not done at Day 5
012-036-005	T	75	12	Treatment	HAMA positive at Day 5 but therapeutic dose still delivered
012-037-003	T	75	12	Treatment	HAMA positive at Day 5, but therapeutic dose still delivered

Study Population

The subjects enrolled in this study had similar baseline entry characteristics to those enrolled in study RIT-II-004 in terms of proportion with transformed disease, distribution of stages of disease, proportion with bulky disease, and prior treatment history, with the

sole exception that all patients must have progressed following treatment with rituximab.

Baseline Entry Characteristics for Study Population **in Study CP 97-012**

Baseline entry characteristic	ITT population n=43
Age (years)	
Median(range)	56 (35-78)
Q1; Q3	49; 65
Gender	
Males (%)	29 (67%)
Race	
Caucasian (%)	35 (81%)
Histologic diagnosis at entry	
W/o transformation	
Low grade	27 (63%)
Intermediate grade	3 (7%)
High grade	0
With transformation	
Low grade	1(2%)
Intermediate grade	12 (28%)
High grade	0
Stage of disease	
I	1 (2%)
II	7 (16%)
III	9 (21%)
IV	26 (61%)
Missing	0
IPI category	
0	2 (5%)
1	12 (28%)
2	15 (35%)
3	5 (12%)
4	4 (9%)
5	1 (2%)
Missing	4 (9%)
Max. tumor diameter	
< 5 cm	24 (56%)
≥ 5, ≤10 cm	14 (33%)
> 10 cm	5 (12%)
# Prior chemo regimens	
Median (range)	4 (1-11)
25^{th}, 75^{th} quartiles	3, 5
# Prior RT regimens	
Median (range)	0 (0-4)
25^{th}, 75^{th} quartiles	0, 1
No Prior BMT	42 (98%)
Time from diagnosis to entry (yrs)	
Median i(range)	4.2 (1.0, 14.2)
25^{th}, 75^{th} quartiles	2.7, 7.0

Efficacy Analyses

No primary efficacy endpoint was identified in the protocol. The analytic plan stated that analyses would be conducted in the intent-to-treat population, which was not further defined. The analytic plan also stated that additional analyses of response rates in patients who completed protocol-specified therapy would also be conducted. In addition, the proposed indicated population to be supported by this study differs from that eligible for the study. For these reasons, all pre-specified analyses were assessed in three populations:

- An intent-to-treat (ITT) population that includes all of the patients registered in the study (n=43). In the ITT analyses, patients who did not receive the tositumomab therapeutic regimen are treated as patients with no response and a response duration of 0 days.

- The "treated" population that includes all patients who received all or part of the tositumomab treatment regimen (n=40);

- The "proposed indication" population that includes patients with rituximab refractory, follicular NHL without major eligibility violations (n=30) The "indicated" population excludes 13 subjects listed below (some subjects are overlapping):

    - 3 subjects who did not receive the tositumomab therapeutic regimen (patients 012-035-005, 012-036-011 & 012-037-013)

    - 5 subjects with prior responses to rituximab that were durable for ≥ 6 months, i.e., were not rituximab-refractory (patients 012-035-001, 012-036-012, 012-037-002, 012-037-007 & 012-037-009)

    - 2 patients who lacked baseline radiographic studies (patients 012-036-002 & 012-036-006),

    - 2 patients without measurable 2 x 2 cm lesions (patients 012-035-005 & 012-037-001)

    - 1 patient who had a treatment within 4 weeks prior to enrollment (012-035-008).

    - 2 patients who did not have follicular histology (012-035-008 and 012-036-002)

    - 2 patients with follicular histology with transformation (012-037-002 and 012-035-015)

Pre-specified Efficacy Analyses

The pre-specified study endpoints were response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. Time to treatment failure was removed as an endpoint in the fourth and final amendment to the protocol. Analyses of time to progression, time to treatment failure, and survival were not provided in FDA's analyses, because these data cannot be interpreted in a study that does not contain an internal control population.

Response Rates and Duration of Response for the Study CP-97-012

	ITT Investigator (n=43)	ITT MIRROR (n=43)	Treated Investigator (n=40)	Treated MIRROR (n=40)	Indicated Invest. assess (n=30)	Indicated MIRROR (n=30)
Overall response rate (Number of responders)	60% (26)	63% (27)	65% (26)	68% (27)	60% (18)	63% (19)
95% CI	44%, 75%	47%, 77%	48%, 79%	51%, 81%	41%, 77%	44%, 80%
Median Duration (Years) (K-M Curves)	1.9	1.3	1.0	1.3	---	2.1 yrs
95% CI on Median	0.9, ---	0.8, ---	0.9, ---	0.8, ---	1.3, …	0.9, ---
IQ Range in Years	0.7, ---	0.8, ---	0.7, ---	0.8, ---	1.3, ---	0.9, ---
Range in Years	0.3, 2.9+	0.1+, 2. 9+	0.3, 2.9+	0.1+, 2.9+	0.3, 2.9+	0.3+, 2.9+
CR (%)	14% (6)	26% (11)	15% (6)	28% (11)	17% (5)	23% (7)
95% CI	5%, 28%	14%, 41%	6%, 30%	15%, 44%	6%, 35%	10%, 42%
CCR (%)	19% (8)	5% (2)	20% (8)	5% (2)	20% (6)	3% (1)
95% CI	8%, 33%	1%, 16%	9%, 36%	1%, 17%	8%, 39%	0%, 17%
PR (%)	28% (12)	33% (14)	30% (12)	35% (14)	23% (7)	37% (11)
95% CI	15%, 44%	19%, 49%	17%, 47%	21%, 52%	10%, 42%	20%, 56%

--- indicates not reached
+ indicates censored

The protocol was amended four times; the last amendment, which stated that efficacy analyses would be conducted according to MIRROR panel assessment, was activated more than one year after the last patient was enrolled. Therefore, it is appropriate to present both the investigator-assessed response rates and that derived from MIRROR panel review. The FDA assessed for concordance between the investigator-assessment and the MIRROR Panel assessment of response (CR + CCR + PR) and non-response (SD + PD). There were no significant differences (p = 1.0, McNemar's test) with only one discrepancy in determination of objective response. However, among the categories of response, the MIRROR panel identified a higher proportion of patients with CR as compared to the investigators; the latter identified a higher proportion of patients with CCR. In analyses where CR and CCR rates are pooled, this difference would not change the analysis.

Other protocol-specified analyses

1. In amendment 1, the analytic plan was revised, stating that analyses of response would be "stratified by response to prior Rituxan." The protocol does not provide additional details on the proposed stratification. For purposes of this analysis, the response rates are analyzed according to patients who responded to rituximab and those who failed to respond to the most recent rituximab regimen. Since rituximab has a long serum half-life and can be detected in the serum 6-9 months after receiving a single 4 weekly course, patients in whom the response to rituximab was less than 6 months should be classified as refractory and analyzed with those who fail to achieve a response. As can be seen in the next table, the response rates to the tositumomab therapeutic regimen does not appear to differ qualitatively in patients who failed to respond to rituximab as compared to those who were responsive, although the duration of response is shorter in the rituximab non-responsive patients.

Response rate to I 131 tositumomab in subsets of the study population based on prior response to rituximab.

Prior response to most recent rituximab regimen	Response to the tositumomab therapeutic regimen	Median Duration of response to the tositumomab therapeutic regimen
Rituximab-responsive (CR, CCR, or PR)	11/18 (61%)	2.1 years
Rituximab non-responsive (PD OR SD)	16/25 (64%)	1.3 years

There were 4 patients enrolled who achieved a CR, CCR or PR to the most recent rituximab course that was durable for ≥ 6 months. The results in these patients whose disease was not refractory to rituximab are summarized as follows:

Patient ID	Rituximab Response	Duration of Response-Rituximab in Years	Tositumomab Therapeutic Regimen Response	Duration of Response-Tositumomab in Years
012-036-001 41F L75B	PR	0.5	PR	0.8
012-036-012 50F L75B	CR	0.6	CR	1.9+
012-037-002 57M T75B	PR	1.2	CR	1.2
012-037-007 58F T75B	CR	1	PR	0.1+
012-037-009 52M L75B	PR	0.6	CR	0.8

2. In amendment 4, the analytic plan in the protocol was modified to an analysis of comparison of the duration of response to the tositumomab therapeutic regimen and to the most recent rituximab regimen

Using the same algorithm as applied in study RIT-II-004, the following table provides a summary of the results for the comparison of response durations for the tositumomab therapeutic regimen and prior rituximab :

Response	Frequency	% of 43
Equivalent response duration	11	26 %
Longer duration with tositumomab	25	58 %
Longer duration with Rituximab	7	16 %

The sign-rank test was used in FDA's analysis because it takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistical change. The proportion of patients for whom the tositumomab therapeutic regimen provided more durable responses was significantly larger (sign-rank test)

The analysis of proportions was performed as follows:

Let p_1 = proportion of responses with equivalent duration to the tositumomab therapeutic regimen and to rituximab
p_2 = proportion of responses with longer duration to the tositumomab therapeutic regimen
p_3 = proportion of responses with longer duration to rituximab

Of interest is a test of the null hypothesis $H_0 : p_2 = p_3$ conditioned on equivalent response, i.e., ignoring equivalent response, and n becomes 32, and test is . $H_0 : p_2 = p_3 = 0.5$ versus $H_1 : p_2 \neq p_3$.
p-value for testing this H_0 was significantly different (two sided, Fisher's exact) in favor of the tositumomab therapeutic regimen

ITT population (n=43)				
		Response to Tositumomab		
		Response	**No Resp**	**Total**
Response to Rituximab	**Response**	11	7	18
	No Resp	16	9	25
	Total	27	16	43

p-value (McNemar) = 0.0719

SAFETY ASSESSMENT

The most frequent adverse events were hematologic toxicities. The incidence of grade 3-4 toxicities were 43%, 25%, and 10% for neutropenia, thrombocytopenia, and anemia, respectively. The most frequent non-hematologic toxicities were asthenia (35%), fever (30%), infection (28%), increased cough (23%), nausea (20%), pain (15%), pneumonia and dyspnea (13% each), vomiting (13%), rash (13%), vomiting (13%), arthralgia (10%) and myalgias (10%). The major organ systems affected were gastrointestinal (43% of patients) and respiratory (40% of patients). Other than the infectious events, most of the non-hematologic toxicity was mild to moderate in severity (NCI CTC grade 1-2). This study is notable for the relatively high rate of infections. A separate summary is provided for the hematologic toxicity, infectious complications, and infusional reactions.

Infusion related AE . The study required pre-medication with acetaminophen and an antihistamine 30 minutes prior to the dosimetric and the therapeutic infusions. Infusion-related AEs were reported in 10% (4/40) of the dosimetric infusions and 20% (8/40) of the therapeutic infusions. The symptom complex of infusion-related AEs includes nausea, chills and fever, pruritus and vomiting; 85% of these were NCI CTC grade 1 or 2. One patient (012-0360001) experienced grade 3 arthralgia, nausea, hypovolemia and vomiting during the therapeutic infusion on day 14. This reaction lasted 5 days and was not described as serious.

Infections: Infection–specific data case report forms were used during the first 12 weeks following the therapeutic dose. Infections were observed in 55% (22/40) of the patients; 22% of the infections were pneumonia 6 patients) and 7% were sepsis (2 patients). Almost all patients, 24/27, received antibiotics. The six cases of pneumonia are outlined below; two of the cases were in the same patient.

Cases of pneumonia

Patient ID	NHL grade	AE grade	Serious AE	Study day	Duration (days)	Therapeutic measures
012-036-010	L	2	No	82	8	Prescription drug(s)
012-035-008	L	3	No	8	9	Prescription drug(s)
012-037-	T	3	Yes	21	15	Prescription drug(s) &

005						**hospitalization**
012-037-006	**I**	**3**	**Yes**	**5**	**8**	**Prescription drug(s) and hospitalization**
012-037-006	**I**	**3**	**No**	**41**	**Na**	**Prescription drug(s)**
012-037-007	**T**	**3**	**No**	**71**	**21**	**Prescription drug(s)**

L =low grade NHL ; T =transformed low grade NHL; I is intermediate grade NHL; Na = not available

Per-Patient Incidence and Duration of Severe Hematologic Toxicity
Study CP 97-012

Hematologic toxicity	
Grade 3-4 neutropenia	43%
Median duration (95% CI)	30 days (18, 43)
Grade 3-4 thrombocytopenia	25%
Median duration (days)	32 days (15, 51)
Grade 3-4 anemia	10%
Median Duration (days)	36 days (16, ---)

Deaths during first 90 study days: Three subjects died during the first 90 study days. Summary precis are given below. One of the patients who died (patient 012-035-008) withdrew from the study shortly after an agent related AE (tumor lysis syndrome). See subject précis in last section of this report.

- 012-035-008: Tumor lysis syndrome, hypoxia, hypercalcemia, death on study day 51.
- 012-036-005: Death on study day 66
- 012-037-005: Death on study day 35 due to aspiration pneumonia

Serious adverse events*:* There were 18 serious adverse events (SAE) reported for 8 patients (20% of the study population). Six of the 8 patients who experienced SAE were enrolled at one study site. Two patients who suffered SAE died prior to study day 90.

Serious Adverse Events

Patient	Study day of SAE	Description SAE
012-035-002	767 804	Myelodysplasia AML
012-035-008	8 16	Hypoxia and tumor lysis syndrome Hypercalcemia

012-037-003	48	Hypercalcemia & acute renal failure
012-037-004	4 32	Severe leg pain Severe leg pain
012-037-005	7 9 19 21 25	Hypercalcemia & respiratory distress Hypotension Staphylococcus septicemia, dyspnea, pleural effusion Cardiac arrhythmias, respiratory distress, pneumonia Right arm deep venous thrombus
012-037-006	5 7	Pneumonia Fever
012-037-011	7 14 20	Anemia Anemia Anemia
012-037-012	88	Abdominal cramps

Narrative Description of Patient Deaths During First 90 Study Days

Patient 012-035-008: A 48 year old male was initially diagnosed with small cell lymphocytic lymphoma with plasmacytoid changes in June 1967. Four courses of chemotherapy included chlorambucil, cyclophosphamide and prednisone, rituximab and cyclophosphamide and fludarabine. At time of entry, the patient had increasing abdominal, inguinal and mediastinal adenopathy, subcutaneous nodules and fatigue, and an LDH of 608 IU/L. The day after the therapeutic dose the patient was diagnosed as having a tumor lysis syndrome manifested by respiratory distress, serum uric acid of 10.6 mg/dL, LDH of 4176. The syndrome was considered probably related to study agent. Hospitalization with aggressive hydration and allopurinal followed. A chest film showed lobe consolidation and pleural effusion. After recovery and discharge from the hospital, the patient was evaluated as having progressive disease and was withdrawn from the study on day 15; he started 3 days later on a chemotherapy regimen and died study day 51.

Patient 012-036-005: A 77 year old male was diagnosed with follicular, small cleaved cell NHL on 10/1992 and received CHOP, CNOP, carmustine and etoposide, fludarabine, interferon, cyclophosphamide, clardribine, and teniposide and rituximab therapies in addition to three courses of radiotherapy to the lower spine. Patient entered study 12/1998. The 7 week assessment disclosed progressive NHL in the chest, abdomen and pelvis by CT; there were new lesions by physical examination. Subject withdrew on study day 49 and died on day 66.

Patient 012-037-005: A 63 year old male was initially diagnosed with follicular, small cleaved lymphoma in October 1998 and treated with courses of MACOP-B, MINE, ESHAP, alpha interferon, EPOCH, methotrexate and cytarabine, ESHAP, liposomal vincristine, rituximab, liposomal atragen, cyclophosphamide and etoposide, and vinblastine, dacarbazine plus 2 courses radiotherapy. When he presented for the therapeutic dose he was disoriented and lethargic; serum calcium was 12.5. A right scapular mass and worsening pleural effusion was related to lymphoma. After improvement the patient was given the therapeutic dose on 4/---/98 and 4 days later noted shortness of breath. During hospitalization blood cultures were positive for Staphylococcus and antibiotics were started. Venous thrombosis of the right arm developed. He died on day 35 of respiratory failure due to aspiration pneumonia.

Narrative Description of Serious Adverse Events

Patient 012-035-002 : A 63 year old male was diagnosed with follicular, mixed small cleaved cell NHL in May 1996. He received courses of fludarabine, cyclophosphamide and rituximab plus one course of radiotherapy. After a partial response the patient withdrew for progressive disease and received additional therapy (not named). September 2000 he reported dyspnea, fatigue. A complete blood count showed low platelets. Myelodysplastic disease was diagnosed following a bone marrow.

Patient 012-035-008: Precis under deaths

Patient 012-037-003: A 66 year old male was diagnosed with follicular, small cleaved cell NHL in 5/1997 and received courses of CHOP,ProMACE-CytoBOM, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine and methotrexate and rituximab. Transformation to diffuse large cell lymphoma was observed. He entered study on 12/1998 and was hospitalized study day 48 because of hypercalcemia and acute renal failure. Calcium was 17 mg/dL. A CT scan showed increased adenopathy. Treatment with furosemide and hydration was started. The patient withdrew from study for progressive disease on the second hospital day and started on fludarabine and dexamethosone. Hydronephrosis of left kidney was observed and considered secondary to lymphadenopathy.

Patient 012-037-004: A 78 year old male was diagnosed with follicular, large cell lymphoma in 2/92 and received CHOP, prednisone, rituximab and cyclophosphamide. Medical history included prostate carcinoma in 1994. Entered study 1/99. Hospitalized on 2/---/99 for nerve block treatment of severe leg pain. He was further treated for the leg pain on 4/---/99 with laminectomy.

Patient 012-037-006: Enrolled on March ---, 1999, received dosimetric dose on April---, 1999. Patient was hospitalized with fever and RLL consolidation (sputum revealed gram positive cocci and rods) on April ---, 1999. The therapeutic dose of 131-I-tositumomab was given on April ---, 1999 (study day 15).

Patient 012-037-006: A 64 year old female was diagnosed with follicular, large cell lymphoma in 2/1996 and received CHOP, interferon, mitoxantrone and prednisone, rituximab, FND and MINE. Entered study in 3/1999. Prior history of asthma and chronic bronchitis . Hospitalized for chest congestion study day 5 and treated for pneumonia [R lower lobe consolidation] with antibiotics. The patient improved with antibiotic therapy, blood cultures were negative and she was discharged on April ---, 1999.

Patient 012-037-011: Patient was enrolled on July --, 1999 with baseline hemoglobin of 6.3 gm/dL, hematocrit of 19.5%, and platelet count of 143,000 cells/µl. He received the dosimetric dose on July ---- and was returned for the therapeutic dose on July ---, 1999. However the dose was withheld when it was noted he had a hemoglobin of 5.8 gm/dL. He then received 2 units of packed RBC.

Patient 012-037-005: see précis under deaths

Patient 012-037- 011: A 52 year old male was diagnosed with follicular, mixed, small-cleaved cell lymphoma in 7/1998 and received CHOP, rituximab, ESHAP. Prior history fatigue and colon polyps. Entered with baseline hemoglobin of 6.3 g/dL . Platelets were

143,000/mm3. Therapeutic dose postponed because of anemia. After red blood cell transfusions, the tositumomab therapeutic regimen was initiated. The therapeutic dose was administered on July 28, 1999. The patient subsequently received additional RBC transfusions on July 29 (2 units) and August 4, 1999 (2 units). Hematocrit was stable between 29-33% from August 11, 1999 through October 26, 1999, without additional transfusions.

Patient 012-037-012: A 36 year old female was diagnosed with follicular small cleaved cell lymphoma (<50% large cells) in June 1997. Prior treatments included CVP, alpha interferon, and rituximab. She was enrolled in this study on July 19, 1999, received the dosimetric infusion on July 29, 1999 and the therapeutic infusion on August 5, 1999 (91.9 mCi; 75 cGy TBI). The patient began complaining of abdominal cramping on study day 88 and was hospitalized on Dec. 2, 1999 for management of abdominal pain, nausea, vomiting and bleeding. Lymphomatous involvement of the small bowel was reported following endoscopy on Dec. 6, 1999. CT of the abdomen on January 26, 2000 revealed increased thickening of the bowel and the patient was withdrawn for progressive disease on Feb. 3, 2000. The patient began CHOP chemotherapy on Feb. 18, 2000.